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NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 09	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced

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=> file biosis
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                        ENTRY     SESSION
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CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 4 September 2002 (20020904/ED)


=> pdx(W)1
PDX(W)1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s pdx(W)1
           328 PDX
       2769592 1
L1          214 PDX(W)1

=> s Idx(W)1
           157 IDX
       2769592 1
L2           38 IDX(W)1

=> s Ipf(W)1
           665 IPF
             7 IPFS
           669 IPF
                 (IPF OR IPFS)
       2769592 1
L3           64 IPF(W)1

=> s stf(W)1
           254 STF
            24 STFS
           268 STF
                 (STF OR STFS)
       2769592 1
L4           45 STF(W)1

=> s pdx1
L5           81 PDX1

=> s idx1
L6            6 IDX1

=> s ipf1
L7           50 IPF1

=> s stf1
L8           18 STF1

=> s islet(W)duodenum(W)homeo?(W)protein(W)1
```

```
         19580 ISLET
         14865 ISLETS
         27897 ISLET
                 (ISLET OR ISLETS)
         16771 DUODENUM
            40 DUODENUMS
           116 DUODENA
         16849 DUODENUM
                 (DUODENUM OR DUODENUMS OR DUODENA)
        994369 HOMEO?
       1234078 PROTEIN
        464105 PROTEINS
       1423261 PROTEIN
                 (PROTEIN OR PROTEINS)
       2769592 1
L9           0 ISLET(W)DUODENUM(W)HOMEO?(W)PROTEIN(W)1

=> s insulin(W)promoter(W)factor(W)1
        196120 INSULIN
           991 INSULINS
        196290 INSULIN
                 (INSULIN OR INSULINS)
         93569 PROMOTER
         23024 PROMOTERS
        102945 PROMOTER
                 (PROMOTER OR PROMOTERS)
        666185 FACTOR
        498806 FACTORS
       1051474 FACTOR
                 (FACTOR OR FACTORS)
       2769592 1
L10         81 INSULIN(W)PROMOTER(W)FACTOR(W)1

=> s somatostatin(W)transcrip?(W)factor(W)1
         24819 SOMATOSTATIN
            95 SOMATOSTATINS
         24839 SOMATOSTATIN
                 (SOMATOSTATIN OR SOMATOSTATINS)
        273003 TRANSCRIP?
        666185 FACTOR
        498806 FACTORS
       1051474 FACTOR
                 (FACTOR OR FACTORS)
       2769592 1
L11          9 SOMATOSTATIN(W)TRANSCRIP?(W)FACTOR(W)1

=> s l1 or l2 or l3 or l4 or l5 or l6 or l7 or l8 or l9 or l10 or l11
L12        454 L1 OR L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11

=> s pancreas
6 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s pancrea?
L13      17696 PANCREA?

=> s duct
=> s duct?
L14      63670 DUCT?

=> s divid
=> s divid? or division or propagat? or proliferat? or mitotic? or mitosis
```

```
        111857 DIVID?
         45962 DIVISION
          9119 DIVISIONS
         52158 DIVISION
                 (DIVISION OR DIVISIONS)
         34208 PROPAGAT?
        215599 PROLIFERAT?
         34186 MITOTIC?
         23295 MITOSIS
          3790 MITOSES
         26106 MITOSIS
                 (MITOSIS OR MITOSES)
L15     434631 DIVID? OR DIVISION OR PROPAGAT? OR PROLIFERAT? OR MITOTIC? OR
               MITOSIS

=> s l12 and l13 and l14 and l15
L16          16 L12 AND L13 AND L14 AND L15

=> save temp
ENTER L#, L# RANGE, ALL, OR (END):l16
ENTER NAME OR (END):idx1/a
ANSWER SET L16 HAS BEEN SAVED AS 'IDX1/A'

=> file ca
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
                                                 18.26      18.47

FULL ESTIMATED COST

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FILE LAST UPDATED: 5 Sep 2002  (20020905/ED)

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=> s l16
           695 PDX
       7055386 I
           157 PDX(W)I
           117 IDX
       7055386 I
            35 IDX(W)I
           351 IPF
            11 IPFS
```

```
    356 IPF
          (IPF OR IPFS)
7055386 1
     58 IPF(W)1
    350 STF
     41 STFS
    375 STF
          (STF OR STFS)
7055386 1
     46 STF(W)1
    149 PDX1
     19 IDX1
     80 IPF1
     34 STF1
  20070 ISLET
  11986 ISLETS
  22753 ISLET
          (ISLET OR ISLETS)
  15382 DUODENUM
     48 DUODENUMS
     98 DUODENA
  15431 DUODENUM
          (DUODENUM OR DUODENUMS OR DUODENA)
  34769 HOMEO?
1397970 PROTEIN
 925628 PROTEINS
1612137 PROTEIN
          (PROTEIN OR PROTEINS)
7055386 1
      0 ISLET(W)DUODENUM(W)HOMEO?(W)PROTEIN(W)1
 139823 INSULIN
   5107 INSULINS
 139917 INSULIN
          (INSULIN OR INSULINS)
 121439 PROMOTER
  42131 PROMOTERS
 138090 PROMOTER
          (PROMOTER OR PROMOTERS)
 710782 FACTOR
 616573 FACTORS
1122846 FACTOR
          (FACTOR OR FACTORS)
7055386 1
     82 INSULIN(W)PROMOTER(W)FACTOR(W)1
  16148 SOMATOSTATIN
    129 SOMATOSTATINS
  16154 SOMATOSTATIN
          (SOMATOSTATIN OR SOMATOSTATINS)
 267101 TRANSCRIP?
 710782 FACTOR
 616573 FACTORS
1122846 FACTOR
          (FACTOR OR FACTORS)
7055386 1
      8 SOMATOSTATIN(W)TRANSCRIP?(W)FACTOR(W)1
  94837 PANCREA?
  94883 DUCT?
 149107 DIVID?
  55853 DIVISION
   3089 DIVISIONS
  59464 DIVISION
          (DIVISION OR DIVISIONS)
 123110 PROPAGAT?
 154870 PROLIFERAT?
```

```
        23240 MITOTIC?
        24306 MITOSIS
         1922 MITOSES
        25365 MITOSIS
                (MITOSIS OR MITOSES)
L17        16 L12 AND L13 AND L14 AND L15

=> duplicate rem
ENTER L# LIST OR (END):l16-l17
DUPLICATE PREFERENCE IS 'BIOSIS, CA'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
                                                    SINCE FILE      TOTAL
COST IN U.S. DOLLARS                                     ENTRY    SESSION
                                                         51.53      70.00
FULL ESTIMATED COST

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PROCESSING COMPLETED FOR L16
PROCESSING COMPLETED FOR L17
L18          21 DUPLICATE REM L16-L17 (11 DUPLICATES REMOVED)

=> d l18 1-21 bib ab

L18  ANSWER 1 OF 21  CA  COPYRIGHT 2002 ACS
AN   136:131238  CA
TI   Bile duct progenitor cells and methods of use
IN   Pang, Kevin; Homa, Monica
PA   USA
SO   U.S. Pat. Appl. Publ., 31 pp., Cont.-in-part of U.S. Ser. No. 973,938.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.         KIND  DATE          APPLICATION NO.   DATE
     ---------------    ----  --------      ---------------   --------
PI   US 2002012653       A1   20020131      US 1997-994539    19971219
     WO 9640872          A1   19961219      WO 1996-US9656    19960607
         W:  AU, CA, JP, KR, US
         RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRAI WO 1996-US9656      W    19960607
     US 1998-973938      A2   19980821
     US 1995-478064      A    19950607
AB   The present invention relates to a substantially pure population of viable
     bile duct progenitor cells, and methods for isolating such
     cells.  The present invention further concerns certain therapeutic uses
     for such progenitor cells, and their progeny.

L18  ANSWER 2 OF 21  CA  COPYRIGHT 2002 ACS
AN   135:24733  CA
TI   Pancreatic stem cells and their use in transplantation
IN   Abraham, Elizabeth J.; Faustman, Denise; Habener, Joel L.; Vallejo, Mario;
     Zulewski, Hendrik
PA   General Hospital Corporation, USA
SO   PCT Int. Appl., 102 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE          APPLICATION NO.   DATE
```

PI	WO 2001039784	A1	20010607	WO 2000-US33031	20001206
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2001024824	A1	20010927	US 2000-731255	20001206
	US 2001046489	A1	20011129	US 2000-731261	20001206
PRAI	US 1999-169082P	P	19991206		
	US 2000-215109P	P	20000628		
	US 2000-238880P	P	20001006		

AB Methods and compns. are described for the treatment of type I insulin-dependent diabetes mellitus and other conditions in a patient using newly identified stem cells that are capable of differentiation into a variety of **pancreatic** islet cells, including insulin-producing beta cells, as well as hepatocytes. Addnl., the patient may be treated with an immunosuppressant agent. Nestin has been identified as a mol. marker for **pancreatic** stem cells, while cytokeratin-19 serves as a marker for a distinct class of islet **ductal** cells. Methods are described whereby nestin-pos. stem cells can be isolated from **pancreatic** islets and cultured to obtain further stem cells or pseudo-islet like structures. Methods for ex vivo differentiation of the **pancreatic** stem cells are disclosed. Methods are described whereby **pancreatic** stem cells can be isolated, expanded, and transplanted into a patient in need thereof, either allogeneically, isogeneically or xenogenically, to provide replacement for lost or damaged insulin-secreting cells or other cells For example, a 3-fold stimulation of nestin mRNA levels in the islets cultured in high glucose compared to the islets cultured in normal glucose was obsd. Similarly, injection of glucagon-like peptide 1 (GLP-1) into mice was found to increase islet mass by 2-fold in 48 h.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1

AN 2002:280266 BIOSIS

DN PREV200200280266

TI **Pancreatic** duodenal homeobox-1, **PDX-1**, a major regulator of beta cell identity and function.

AU McKinnon, C. M.; Docherty, K. (1)

CS (1) Department of Molecular and Cell Biology, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD: k.docherty@aberdeen.ac.uk UK

SO Diabetologia, (October, 2001) Vol. 44, No. 10, pp. 1203-1214. print. ISSN: 0012-186X.

DT General Review

LA English

AB **Pancreatic** duodenal homeobox -1 is a transcription factor that is expressed in beta and delta cells of the islets of Langerhans and in dispersed endocrine cells of the duodenum. It is involved in regulating the expression of a number of key beta-cell genes as well as somatostatin. It also plays a pivotal part in the development of the **pancreas** and islet cell ontogeny. Thus homozygous disruption of the gene in mice and humans results in **pancreatic** agenesis. Heterozygous mutations in the gene result in impaired glucose tolerance and symptoms of diabetes as seen in MODY4 and late-onset Type II (non-insulin-dependent) diabetes mellitus. In adults **pancreatic** duodenal homeobox-1 expression is increased in **duct** cells of the **pancreas**

that have been induced to **proliferate** and differentiate to form new islets. Defects in **pancreatic** duodenal homeobox-1 could therefore contribute to Type II diabetes by affecting compensatory mechanisms that increase the rate of beta-cell neogenesis to meet the increased insulin secretory demand. It could also be a pharmacological target for beta-cell defects in Type II diabetes, while its role as a regulator of islet stem cell activity is being exploited to produce a replenishable source of islet tissue for transplantation in Type I (insulin-dependent) diabetes mellitus.

L18 ANSWER 4 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 2001:142229 BIOSIS
DN PREV200100142229
TI PDX:PBX complexes are required for normal **proliferation** of **pancreatic** cells during development.
AU Dutta, Sanjoy; Gannon, Maureen; Peers, Bernard; Wright, Chris; Bonner-Weir, Susan; Montminy, Marc (1)
CS (1) Clayton Laboratories for Peptide Biology, Salk Institute, 10010 North Torrey Pines Road, La Jolla, CA, 92037: montminy@salk.edu USA
SO Proceedings of the National Academy of Sciences of the United States of America, (January 30, 2001) Vol. 98, No. 3, pp. 1065-1070. print. ISSN: 0027-8424.
DT Article
LA English
SL English
AB The homeobox factor **PDX-1** is a key regulator of **pancreatic** morphogenesis and glucose homeostasis; targeted disruption of the **PDX-1** gene leads to **pancreatic** agenesis in **pdx-1**(-/-) homozygotes. **Pdx-1** heterozygotes develop normally, but they display glucose intolerance in adulthood. Like certain other homeobox proteins, **PDX-1** contains a consensus FPWMK motif that promotes heterodimer formation with the ubiquitous homeodomain protein PBX. To evaluate the importance of **PDX-1**:PBX complexes in **pancreatic** morphogenesis and glucose homeostasis, we expressed either wild-type or PBX interaction defective **PDX-1** transgenes under control of the **PDX-1** promoter. Both wild-type and mutant **PDX-1** transgenes corrected glucose intolerance in **pdx-1** heterozygotes. The wild-type **PDX-1** transgene rescued the development of all **pancreatic** lineages in **pdx-1**(-/-) animals, and these mice survived to adulthood. In contrast, **pancreata** from **pdx-1**(-/-) mice expressing the mutant **PDX-1** transgene were hypoplastic, and these mice died within 3 weeks of birth from **pancreatic** insufficiency. All **pancreatic** cell types were observed in **pdx-1**(-/-) mice expressing the mutant **PDX-1** transgene; but the islets were smaller, and increased numbers of islet hormone-positive cells were noted within the **ductal** epithelium. These results indicate that **PDX-1**:PBX complexes are dispensable for glucose homeostasis and for differentiation of stem cells into **ductal**, endocrine, and acinar lineages; but they are essential for expansion of these populations during development.

L18 ANSWER 5 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
AN 2001:214765 BIOSIS
DN PREV200100314765
TI Multipotential nestin-positive stem cells isolated from adult **pancreatic** islets differentiate ex vivo into **pancreatic** endocrine, exocrine, and hepatic phenotypes
AU Zulewski, Henryk; Abraham, Elizabeth J.; Gerlach, Melissa J.; Daniel, Philip B.; Moritz, Wolfgang; Muller, Beat; Vallejo, Mario; Thomas, Melissa

K.; Habener, Joel F. (1)
CS (1) Laboratory of Molecular Endocrinology, Massachusetts General Hospital, 55 Fruit St., WEL320, Boston, MA, 02114: jhabener@partners.org USA
SO Diabetes, (March, 2001) Vol. 50, No. 3, pp. 521-533. print.
ISSN: 0012-1797.
DT Article
LA English
SL English
AB The endocrine cells of the rat **pancreatic** islets of Langerhans, including insulin-producing beta-cells, turn over every 40-50 days by processes of apoptosis and the **proliferation** and differentiation of new islet cells (neo-genesis) from progenitor epithelial cells located in the **pancreatic ducts**. However, the administration to rats of islet trophic factors such as glucose or glucagon-like peptide 1 for 48 h results in a doubling of islet cell mass, suggesting that islet progenitor cells may reside within the islets themselves. Here we show that rat and human **pancreatic** islets contain a heretofore unrecognized distinct population of cells that express the neural stem cell-specific marker nestin. Nestin-positive cells within **pancreatic** islets express neither the hormones insulin, glucagon, somatostatin, or **pancreatic** polypeptide nor the markers of vascular endothelium or neurons, such as collagen IV and galanin. Focal regions of nestin-positive cells are also identified in large, small, and centrolobular **ducts** of the rat **pancreas**. Nestin-positive cells in the islets and in **pancreatic ducts** are distinct from **ductal** epithelium because they do not express the **ductal** marker cytokeratin 19 (CK19). After their isolation, these nestin-positive cells have an unusually extended **proliferative** capacity when cultured in vitro (apprx8 months), can be cloned repeatedly, and appear to be multipotential. Upon confluence, they are able to differentiate into cells that express liver and exocrine **pancreas** markers, such as alpha-fetoprotein and **pancreatic** amylase, and display a **ductal**/endocrine phenotype with expression of CK19, neural-specific cell adhesion molecule, insulin, glucagon, and the **pancreas**/duodenum specific homeodomain transcription factor, **IDX-1**. We propose that these nestin-positive islet-derived progenitor (NIP) cells are a distinct population of cells that reside within **pancreatic** islets and may participate in the neogenesis of islet endocrine cells. The NIP cells that also reside in the **pancreatic ducts** may be contributors to the established location of islet progenitor cells. The identification of NIP cells within the **pancreatic** islets themselves suggest possibilities for treatment of diabetes, whereby NIP cells isolated from **pancreas** biopsies could be expanded ex vivo and transplanted into the donor/recipient.

L18 ANSWER 6 OF 21 CA COPYRIGHT 2002 ACS
AN 133:38709 CA
TI An animal model for identifying a common stem/progenitor to liver cells and **pancreatic** cells
IN Sarvetnick, Nora; Krakowski, Michelle L.; Kritzik, Marcie R.
PA The Scripps Research Institute, USA
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000036091	A2	20000622	WO 1999-US29490	19991213
	WO 2000036091	A3	20001109		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,

MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1141247 A2 20011010 EP 1999-967280 19991213
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

US 2001013134 A1 20010809 US 2001-826779 20010405
PRAI US 1998-212531 A2 19981216
WO 1999-US29490 W 19991213

AB The invention provides animal models, where the ectopic expression of KGF, EGF, or both is under the control of a **pancreas**-specific promoter, e.g., the insulin promoter. The expression of KGF in the ins-KGF **pancreatic** islets of Langerhans results in enlarged islets, with substantial **proliferation** of **duct** cells within the islet mass, and the presence of albumin and alpha-fetoprotein-producing hepatocytes in the islets of the ins-KGF **pancreata**. The compns. and methods disclosed are useful for identifying and isolating **pancreatic** stem/progenitor cells, including a common stem/progenitor to liver cells and **pancreatic** cells.

L18 ANSWER 7 OF 21 CA COPYRIGHT 2002 ACS
AN 135:301720 CA
TI Human **pancreatic** stem cell and diabetes cell therapy
AU Pattou, Francois; Kerr-Conte, Julie; Gmyr, Valery; Vandewalle, Brigitte; Vantyghem, Marie-Christine; Lecomte-Houcke, Martine; Proye, Charles; Lefebvre, Jean
CS Hospitalo-Universitaire, UPRES 1048 de Universite de Lille 2 et Service de Chirurgie Generale et Endocrinienne, Centre Hospitalier, Universitaire de Lille, Lille, F59037, Fr.
SO Bulletin de l'Academie Nationale de Medecine (Paris, France) (2000), 184(9), 1887-1901
CODEN: BANMAC; ISSN: 0001-4079
PB Academie Nationale de Medecine
DT Journal; General Review
LA French
AB A review, with refs. Cell therapy offers today important perspectives for the treatment of type 1 diabetes. The current utilization of primary human islets of Langerhans nevertheless forbids all hope of developing this treatment on a large scale. The recent description of the persistence of stem cells capable of **proliferating** and differentiating in the adult **pancreas** offers an attractive alternative for the prodn. in vitro of homologous insulin-secreting cells. We first reproduced in vitro from human islet prepns. the **proliferation** of **ductal** epithelial structures and their progressive organization. Thereafter, we focused on the description of a reproducible source of human **ductal** cells by the transdifferentiation of exocrine prepns. More recently we described in these exocrine derived **ductal** cells the expression the of **insulin promoter factor-1** (**IPF-1**/otherwise known as **PDX-1**), a transcription factor essential for the differentiation of **ductal** cells into endocrine cells during both development and **pancreatic** regeneration. If the **proliferation** and differentiation of these cells is confirmed, this approach could lead to the description of an abundant source of human **pancreatic** stem cells for the prodn. ex vivo of human insulin secreting cells and may even allow autologous cell therapy, in the absence of immunosuppression.
RE CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 8 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
AN 2001:267534 BIOSIS
DN PREV200100267534
TI Adult human cytokeratin 19-positive cells reexpress **insulin promoter factor 1** in vitro: Further evidence for pluripotent **pancreatic** stem cells in humans.
AU Gmyr, Valery; Kerr-Conte, Julie (1); Belaich, Sandrine; Vandewalle, Brigitte; Leteurtre, Emmanuelle; Vantyghem, Marie Christine; Lecomte-Houcke, Martine; Proye, Charles; Lefebvre, Jean; Pattou, Francois
CS (1) Laboratory of Cell Culture, University Hospital Center of Lille, 1 Place de Verdun, Lille, 59045: jkerr-conte@univ-lille2.fr France
SO Diabetes, (October, 2000) Vol. 49, No. 10, pp. 1671-1680. print. ISSN: 0012-1797.
DT Article
LA English
SL English
AB Human **pancreatic** cells with a typical **ductal** phenotype and potential to **proliferate** can be obtained in vitro, but the differentiation capacity of these putative human **pancreatic** stem cells remains to be documented. We investigated the protein and mRNA expression of **insulin promoter factor 1** (**IPF-1**) (or **pancreas**/duodenal homeobox 1), a transcription factor critical for **pancreatic** development and endocrine cell neogenesis, in human **pancreatic** **ductal** cells derived from cultured exocrine tissue. In vitro, exocrine cells rapidly adhered (within 12 h) and were de-/transdifferentiated to **ductal** cells after 3 days with a dramatic loss of amylase protein (n = 4, 92 +- 3.3%, P < 0.05 vs. day 1) and a simultaneous increase of **ductal** cytokeratin 19 protein (n = 4, 3.4-fold on day 3 and 7-fold on day 9, P < 0.05 vs. day 1). **IPF-1** protein and mRNA levels were low to undetectable in exocrine preparations before culture. After 2 days of culture, a 3.2-fold increase in **IPF-1** protein was observed, corresponding to the characteristic 46-kDa protein in Western blots. Reverse transcriptase-polymerase chain reaction confirmed a 10.5-fold increase in **IPF-1** mRNA levels after 3 days of culture (n = 5, P < 0.001 vs. day 1). Double immunocytochemistry showed direct evidence that **IPF-1** appeared during culture in these exocrine-derived **ductal** cells (cytokeratin 7-positive) and was not merely in contaminating endocrine cells (chromogranin A-positive). In conclusion, we describe herein the first converging evidence on both the molecular and protein level that human cells with a typical **ductal** phenotype derived ex vivo from **pancreatic** exocrine tissue (obtained from healthy donors) can reexpress **IPF-1** in culture, suggesting their **pancreatic** precursor/stem cell potential.

L18 ANSWER 9 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
AN 2000:377198 BIOSIS
DN PREV200000377198
TI Modulation of rat **pancreatic** acinoductal transdifferentiation and expression of **PDX-1** in vitro.
AU Rooman, I.; Heremans, Y.; Heimberg, H.; Bouwens, L. (1)
CS (1) Department of Experimental Pathology, VUB, Laarbeeklaan 103, B-1090, Brussels Belgium
SO Diabetologia, (July, 2000) Vol. 43, No. 7, pp. 907-914. print. ISSN: 0012-186X.
DT Article
LA English
SL English
AB Aims/hypothesis: In adult **pancreatic** regeneration models exocrine acini are found to transdifferentiate to **duct**-like

complexes. This has also been associated with the formation of new endocrine islet cells. We aimed to establish an in vitro model in which this transdifferentiation process is characterised and can be modulated. Methods: Purified rat **pancreatic** acini were cultured in suspension. Differentiation was analysed by immunocytochemistry, electron microscopy, western blotting and RT-PCR. Results: During culture acinar cells directly transdifferentiated without **dividing**, the cells lost their acinar phenotype and started to express cytokeratins 20 and 7 and fetal liver kinase-1 (Flk-1) receptors for vascular endothelial growth factor. Expression of the acinar **pancreatic** exocrine transcription factor (PTF-1) remained and the **pancreatic** duodenal homeobox-containing transcription factor (**PDX-1**) was induced. When transdifferentiation was completed, the cells started to express protein gene product 9.5, a panneuroendocrine marker. By combining these features, the transdifferentiated cells show similar characteristics to precursor cells during active beta-cell neogenesis. We were able to modulate the differentiation state by addition of nicotinamide or sodium butyrate, agents which are known to stimulate endocrine differentiation in other models. Conclusion/interpretation: Here, we present an in vitro system in which the cellular differentiation of putative **pancreatic** endocrine precursor cells and their **PDX-1** expression can be modulated, thereby providing a possible model for the study of beta-cell transdifferentiation.

L18 ANSWER 10 OF 21 CA COPYRIGHT 2002 ACS
AN 133:84532 CA
TI Insulinotropic glucagon-like peptide 1 agonists stimulate expression of homeodomain protein **IDX-1** and increase islet size in mouse **pancreas**
AU Stoffers, Doris A.; Kieffer, Timothy J.; Hussain, Mehboob A.; Drucker, Daniel J.; Bonner-Weir, Susan; Habener, Joel F.; Egan, Josephine M.
CS Division of Endocrinology, Diabetes and Metabolism, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
SO Diabetes (2000), 49(5), 741-748
CODEN: DIABAZ; ISSN: 0012-1797
PB American Diabetes Association
DT Journal
LA English
AB Diabetes is caused by a failure of the **pancreas** to produce insulin in amts. sufficient to meet the body's needs. A hallmark of diabetes is an abs. (type 1) or relative (type 2) redn. in the mass of **pancreatic** .beta.-cells that produce insulin. Mature .beta.-cells have a life-span of .apprx.48-56 days (rat) and are replaced by the replication of preexisting .beta.-cells and by the differentiation and **proliferation** of new .beta.-cells (neogenesis) derived from the **pancreatic ducts**. The insulinotropic hormone glucagon-like peptide (GLP)-1, which is produced by the intestine, enhances the **pancreatic** expression of the homeodomain transcription factor **IDX-1** that is crit. for **pancreas** development and the transcriptional regulation of the insulin gene. Concomitantly, GLP-1 administered to diabetic mice stimulates insulin secretion and effectively lowers their blood sugar levels. GLP-1 also enhances .beta.-cell neogenesis and islet size. Thus, in addn. to stimulating insulin secretion, GLP-1 stimulates the expression of the transcription factor **IDX-1** while stimulating .beta.-cell neogenesis and may thereby be an effective treatment for diabetes.
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 11 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:28563 BIOSIS
DN PREV200100028563
TI Hydrolysed casein diet protects BB rats from developing diabetes by

promoting islet neogenesis.

AU Wang, Gen-Sheng; Gruber, Heidi; Smyth, Peter; Pulido, Olga; Rosenberg, Lawrence; Duguid, William; Scott, Fraser W. (1)

CS (1) Laboratory N1, Ottawa Hospital Research Institute, Ottawa Hospital-General Campus, 501 Smyth Road, Ottawa, ON, K1H 8L6: fscott@ottawahospital.on.ca Canada

SO Journal of Autoimmunity, (Dec., 2000) Vol. 15, No. 4, pp. 407-416. print. ISSN: 0896-8411.

DT Article

LA English

SL English

AB Feeding diabetes-prone BioBreeding (BBdp) rats a hydrolysed-casein (HC)-based semi-purified diet results in two-to-three-fold fewer diabetes cases compared with feeding cereal-based diets such as NIH-07 (NIH). We showed previously that young NIH-fed BBdp rats had decreased islet area at a time when classic insulitis was minimal. Rats fed an HC diet maintained near normal islet area followed 3-4 weeks later by a deviation of the **pancreas** cytokine pattern from Th1 to Th2/Th3. This finding raised the possibility that BBdp rats were more susceptible to diet-induced changes in islet homeostasis. To investigate this possibility further, BBdp rats were fed an NIH or HC diet from days 23 to 45. Bouin's fixed sections of **pancreas** were stained with H & E or antibodies for insulin and glucagon. Cell **proliferation** nuclear antigen (PCNA) was used as a marker of cell **proliferation** and cells were stained for putative markers of islet neogenesis, cytokeratin 20 (CK20) and Bcl-2. Apoptotic bodies were recognized by morphological features and by TUNEL-positive staining. BBdp rats fed an HC diet had a significantly higher beta-cell fraction than rats fed NIH, whereas alpha-cell fraction and beta-cell size were not affected by diet or rat type. Apoptotic bodies of beta-cells were rare and unaffected by diet. The number of PCNA+ beta-cells was not affected by diet. CK20 expression was localized in the **ductular** system and at the periphery of islets in rats aged 7 and 45 days. There were more CK20+ islets in BBdp rats fed NIH than in those fed HC but the CK20 area fraction was unaffected by diet. Bcl-2 expression was scattered among **ducts** and central acinar cells. The number of extra-islet insulin+ and glucagon+ clusters (<four cells) was significantly higher in animals fed the HC diet compared with those fed NIH. Most of the insulin+ clusters were also homeodomain-containing transcription factor **pancreas** duodenum homeobox gene-1 (**PDX-1**) positive. Glucagon+/**PDX-1**+ clusters were rarely found. These data are consistent with a shift in **pancreas** homeostasis that maintains islet cell mass by increased islet neogenesis, a process that was enhanced in animals fed a diabetes-retardant diet.

L18 ANSWER 12 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6

AN 2000:216835 BIOSIS

DN PREV200000216835

TI Diabetes and **pancreatic** tumours in transgenic mice expressing Pa X 6.

AU Yamaoka, T. (1); Yano, M.; Yamada, T.; Matsushita, T.; Moritani, M.; Ii, S.; Yoshimoto, K.; Hata, J.; Itakura, M.

CS (1) Otsuka Department of Molecular Nutrition, School of Medicine, University of Tokushima, Tokushima, 770-8503 Japan

SO Diabetologia, (March, 2000) Vol. 43, No. 3, pp. 332-339. ISSN: 0012-186X.

DT Article

LA English

SL English

AB Aims/hypothesis: Both endocrine and exocrine cells of the **pancreas** differentiate from epithelial cells of primitive **pancreatic** **ducts**, and four types of **pancreatic** islet cells (alpha, beta, delta, and PP cells) are derived from the common pluripotent

precursor cells. Although Pa X 6 is expressed in all islet cells, Pa X 4 is detected only in beta cells. In homozygous Pa X 4-null mice, beta cells are absent, whereas the number of alpha cells is increased. Therefore, we hypothesized that the balance of Pa X 4 and 6 is one of the determinants by which the common progenitor cells differentiate into alpha or beta cells. Methods: To change this balance, we generated transgenic mice overexpressing Pa X 6 driven by the insulin promoter or the **PDX1** promoter. Results: In both types of transgenic mice, normal development of beta cells was disturbed, resulting in apoptosis of beta cells and diabetes. In Insulin/Pa X 6-Tg mice, beta cells were specifically affected, whereas in PDX/Pa X 6-Tg mice, developmental abnormalities involved the whole **pancreas** including hypoplasia of the exocrine **pancreas**. Furthermore, PDX/Pa X 6-Tg mice experienced **proliferation** of both **ductal** epithelia and islet cells and subsequent cystic adenoma of the **pancreas**. Conclusion/interpretation: These findings suggest that Pa X 6 promotes the growth of **ductal** epithelia and endocrine progenitor cells and that the suppression of Pa X 6 is necessary for the normal development of beta cells and the exocrine **pancreas**.

AN 2000:59802 BIOSIS
DN PREV200000059802
TI Expansion of **Pdx1**-expressing **pancreatic** epithelium and islet neogenesis in transgenic mice overexpressing transforming growth factor alpha.
AU Song, Si Young; Gannon, Maureen; Washington, M. K.; Scoggins, Charles R.; Meszoely, Ingrid M.; Goldenring, James R.; Marino, Christopher R.; Sandgren, Eric P.; Coffey, Robert J., Jr.; Wright, Christopher V. E.; Leach, Steven D (1)
CS (1) Division of Surgical Oncology, T-2104 Medical Center North, Vanderbilt University Medical Center, 21st and Garland Streets, Nashville, TN USA
SO Gastroenterology, (Dec., 1999) Vol. 117, No. 6, pp. 1416-1426. ISSN: 0016-5085.
DT Article
LA English
SL English
AB Background & Aims: The progenitor cells responsible for transforming growth factor (TGF)-alpha-induced **pancreatic ductal** metaplasia and neoplasia remain uncharacterized. During **pancreatic** development, differentiated cell types arise from **ductal** progenitor cells expressing the **Pdx1** homeodomain transcription factor. The aims of this study were, first, to evaluate the role of **Pdx1**-expressing stem cells in MT-TGFalpha transgenic mice, and second, to further characterize cell **proliferation** and differentiation in this model. Methods: To assess **Pdx1** gene expression in normal and metaplastic epithelium, we performed in vivo reporter gene analysis using heterozygous Pdx1lacZ/+ and bigenic Pdx1lacZ/+/MT-TGFalpha mice. Results: Pdx1lacZ/+/MT-TGFalpha bigenics showed up-regulated **Pdx1** expression in premalignant metaplastic **ductal** epithelium. In addition to **Pdx1** gene activation, TGF-alpha-induced metaplastic epithelium demonstrated a pluripotent differentiation capacity, as evidenced by focal expression of Pax6 and initiation of islet cell neogenesis. The majority of **Pdx1**-positive epithelial cells showed no expression of insulin, similar to the pattern observed during embryonic development. Conclusions: Overexpression of TGF-alpha induces expansion of a **Pdx1**-expressing epithelium characterized by focal expression of Pax6 and initiation of islet neogenesis. These findings suggest that premalignant events induced by TGF-alpha in mouse **pancreas** may recapitulate a developmental program active during embryogenesis.

AN 1999:324535 BIOSIS

DN PREV199900324535
TI Activation of the **Pdx1** homeobox gene during TGFa-induced premalignant **pancreatic ductal proliferation** : In vivo reporter gene analysis using "double transgenic" mice.
AU Song, Si Young (1); Gannon, Maureen (1); Meszoely, Ingrid M. (1); Scoggins, Charles R. (1); Yang, LiYing (1); Wright, Christopher V. E. (1); Coffey, Robert J. (1); Leach, S. D.
CS (1) Vanderbilt Univ Med Ctr, Nashville, TN USA
SO Gastroenterology, (April, 1999) Vol. 116, No. 4 PART 2, pp. A1164. Meeting Info.: Digestive Disease Week and the 100th Annual Meeting of the American Gastroenterological Association Orlando, Florida, USA May 16-19, 1999 American Gastroenterological Association . ISSN: 0016-5085.
DT Conference
LA English

L18 ANSWER 15 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:293778 BIOSIS
DN PREV199900293778
TI Sustained **proliferation** of **PDX-1**+ cells derived from human islets.
AU Beattie, Gillian M.; Itkin-Ansari, Pamela; Cirulli, Vincenzo; Leibowitz, Gil; Lopez, Ana D.; Bossie, Stuart; Mally, Martin I.; Levine, Fred; Hayek, Alberto (1)
CS (1) Islet Research Laboratory, Department of Pediatrics, UCSD, 9894 Genesee Ave., La Jolla, CA, 92037 USA
SO Diabetes, (May, 1999) Vol. 48, No. 5, pp. 1013-1019. ISSN: 0012-1797.
DT Article
LA English
SL English
AB Ex vivo expansion of human beta-cells is an important step toward the development of cell-based insulin delivery systems in type 1 diabetes. Here, we report that human **pancreatic** endocrine cells can be expanded through 15 cell doublings in vitro for an estimated total 30,000-fold increase in cell number. We believe that the cells resulting from these cultures are of beta-cell origin, since they uniformly express the transcription factor **PDX-1** (**STF-1**, **IDX-1**, **IPF-1**), which is initially seen only in cells positive for insulin and negative for the **ductal** cell marker cytokeratin (CK)-19. To rule out the possibility that **PDX-1** expression might be induced by the culture conditions used here, cells from isolated human **pancreatic ducts** were cultured under the same conditions as the islet cells. Cells in these cultures expressed CK-19 but not **PDX-1**. Although the expanded beta-cells continued to express **PDX-1**, insulin expression was lost over time. Whether reexpression of islet-specific genes in vitro is essential for successful cell transplantation remains to be determined.

L18 ANSWER 16 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7
AN 2000:95419 BIOSIS
DN PREV200000095419
TI **PDX-1** and Msx-2 expression in the regenerating and developing **pancreas**
AU Kritzik, M. R.; Jones, E.; Chen, Z.; Krakowski, M.; Krahl, T.; Good, A.; Wright, C.; Fox, H.; Sarvetnick, N. (1)
CS (1) Department of Immunology, Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA, 92037 USA
SO Journal of Endocrinology, (Dec., 1999) Vol. 163, No. 3, pp. 523-530. ISSN: 0022-0795
DT Article
LA English

SL English
AB We have observed **pancreatic duct** cell **proliferation** and islet regeneration in transgenic mice whose **pancreata** produce interferon gamma (IFNg mice). We have previously demonstrated that new islet cells derive from endocrine progenitor cells in the **pancreatic ducts** of this model. The current study was initiated to define these endocrine progenitor cells further and to identify novel markers associated with **pancreatic** regeneration. Importantly, we have found that **PDX-1**, a transcription factor required for insulin gene transcription as well as for **pancreatic** development during embryogenesis, is expressed in the **duct** cells of IFNg mice. This striking observation suggests an important role for **PDX-1** in the marked regeneration observed in IFNg mice, paralleling its critical function during ontogeny. Also demonstrated was elevated expression of the homeobox-containing protein Msx-2 in the **pancreata** of fetal mice as well as in adult IFNg mice, identifying this molecule as a novel marker associated with **pancreatic** development and regeneration as well. The identification of **PDX-1** and Msx in the **ducts** of the IFNg transgenic **pancreas** but not in the **ducts** of the non-transgenic **pancreas** suggests that these molecules are associated with endocrine precursor cells in the **ducts** of the IFNg transgenic mouse.

L18 ANSWER 17 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 8
AN 1999:153690 BIOSIS
DN PREV199900153690
TI The homeodomain protein **IDX-1** increases after an early burst of **proliferation** during **pancreatic** regeneration.
AU Sharma, Arun; Zangen, David H.; Reitz, Petra; Taneja, Monica; Lissauer, Matthew E.; Miller, Christopher P.; Weir, Gordon C.; Habener, Joel F.; Bonner-Weir, Susan (1)
CS (1) Joslin Diabetes Cent., One Joslin Pl., Boston, MA 02215 USA
SO Diabetes, (March, 1999) Vol. 48, No. 3, pp. 507-513.
ISSN: 0012-1797.
DT Article
LA English
AB Islet duodenal homeobox 1 (**IDX-1**/**IPF-1**/**STF-1**/**PDX-1**), a homeodomain protein that transactivates the insulin promoter, has been shown by targeted gene ablation to be required for **pancreatic** development. After 90% **pancreatectomy** (Px), the adult **pancreas** regenerates in a process recapitulating embryonic development, starting with a burst of **proliferation** in the epithelium of the common **pancreatic duct**. In this model, **IDX-1** mRNA was detected by semiquantitative reverse transcription-polymerase chain reaction in total RNA from isolated common **pancreatic ducts** at levels 10% of those of isolated islets. The **IDX-1** mRNA levels were not significantly different for common **pancreatic ducts** of Px, sham Px, and unoperated rats and did not change with time after surgery. By immunoblot analysis, **IDX-1** protein was only faintly detected in these **ducts** 1 and 7 days after Px or sham Px but was easily detected at 2 and 3 days after Px. Similarly, **IDX-1** immunostaining was barely detectable in sham or unoperated **ducts** but was strong in **ducts** at 2-3 days after Px. The increase of **IDX-1** immunostaining followed that of BrdU incorporation (**proliferation**). These results indicate a posttranscriptional regulation of the **IDX-1** expression in **ducts**. In addition, islets isolated 3-7 d after Px showed higher **IDX-1** protein expression than control islets. Thus, in **pancreatic** regeneration **IDX-1** is upregulated in newly **divided ductal** cells

as well as in islets. The timing of enhanced expression of **IDX-1** implies that **IDX-1** is not important in the initiation of regeneration but may be involved in the differentiation of **ductal** cells to beta-cells.

L18 ANSWER 18 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:289195 BIOSIS
DN PREV199900289195
TI Ontogeny of peptide growth factor and transcription factor expression during induced islet cell neogenesis in the neonatal rat **pancreas**.
AU Arany, E. (1); Strutt, B.; Duvillie, B.; Hill, D. J.
CS (1) Lawson Research Institute, St Joseph's Health Centre, University of Western Ontario, London, Ontario, N6A 4V2 Canada
SO Journal of Endocrinology, (March, 1999) Vol. 160, No. SUPPL., pp. P124. Meeting Info.: 18th Joint Meeting of the British Endocrine Societies Bournemouth, England, UK April 12-15, 1999 British Endocrine Societies . ISSN: 0022-0795.
DT Conference
LA English

L18 ANSWER 19 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 9
AN 1997:390039 BIOSIS
DN PREV199799689242
TI Demonstration of two different processes of beta-cell regeneration in a new diabetic mouse model induced by selective perfusion of alloxan.
AU Waguri, Masako (1); Yamamoto, Koji; Miyagawa, Jun-Ichiro; Tochino, Yoshihiro; Yamamori, Katsumi; Fajimoto, Yoshitaka; Nakajima, Hiromu; Watada, Hirotaka; Yoshiuchi, Issei; Itoh, Naoto; Imagawa, Akihisa; Namba, Mitsuyoshi; Kuwajima, Masamichi; Yamasaki, Yoshimitsu; Hanafusa, Toshiaki; Matsuzawa, Yuji
CS (1) Second Dep. Intern. Med., Osaka Univ. Med. Sch., 2-2 Yamada-oka, Suita, Osaka 565 Japan
SO Diabetes, (1997) Vol. 46, No. 8, pp. 1281-1290. ISSN: 0012-1797.
DT Article
LA English
AB To clarify the regeneration process of **pancreatic** beta-cells, we established a new mouse model of diabetes induced by selective perfusion of alloxan after clamping the superior mesenteric artery. In this model, diabetes could be induced by the destruction of beta-cells in alloxan-perfused segments, while beta-cells in nonperfused segments were spared. Intraperitoneal glucose tolerance tests showed glucose intolerance, which gradually ameliorated and was completely normalized in 1 year with a concomitant increase of insulin content in the **pancreas**. Histological examination showed neo-islet formation in the alloxan-perfused segment and the **proliferation** of spared beta-cells in the nonperfused segment. In the alloxan-perfused segment, despite a marked reduction of islets in size and number at an early stage, both the number of islets, including islet-like cell clusters (ICCs), and the relative islet area significantly increased at a later stage. Increased single beta-cells and ICCs were located in close contact with **duct** cell lining, suggesting that they differentiated from **duct** cells and that such extra-islet precursor cells may be important for beta-cell regeneration in beta-cell-depleted segment. In addition to beta cells, some nonhormone cells in ICCs were positive for nuclear **insulin promoter factor 1**, which indicated that most, if not all, nonhormone cells positive for this factor were beta-cell precursors. In the nonperfused segment, the islet area increased significantly, and the highest 5-bromo-2-deoxyuridine-labeling index in beta-cells was observed at day 5, while the number of islets did not increase significantly. This indicated that the regeneration of islet endocrine cells occurs mostly through the

proliferation of preexisting intra-islet beta-cells in the nonperfused segment. In conclusion, the regeneration process of beta-cells varied by circumstance. Our mouse model is useful for studying the mechanism of regeneration, since differentiation and **proliferation** could be analyzed separately in one **pancreas**.

L18 ANSWER 20 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 10
AN 1997:202299 BIOSIS
DN PREV199799501502
TI Alpha-Cell neogenesis in an animal model of IDDM.
AU O'Reilly, Lorraine A.; Gu, Danling; Sarvetnick, Nora; Edlund, Helena; Phillips, Jenny M.; Fulford, Tony; Cooke, Anne (1)
CS (1) Dep. Pathology, Immunology Div., Univ. Cambridge, Tennis Court Road, Cambridge CB2 1QP UK
SO Diabetes, (1997) Vol. 46, No. 4, pp. 599-606.
ISSN: 0012-1797.
DT Article
LA English
AB Currently there is debate regarding the capacity of **pancreatic** islets to regenerate in adult animals. Because **pancreatic** endocrine cells are thought to arise from **duct** cells, we examined the **pancreatic ductal** epithelium of the diabetic NOD mouse for evidence of islet neogenesis. We have evidence of **duct proliferation** as well as **ductal** cell differentiation, as suggested by bromodeoxyuridine-labeling and the presence of glucagon-containing cells within these **ducts**. In addition, the **ductal** epithelia in diabetic NOD mice expressed the neuroendocrine markers neuropeptide Y and tyrosine hydroxylase. These **ducts** also expressed the homeobox gene product, insulin promoter factor 1. **Ductal** cell **proliferation** and expression of these markers was not observed in transgenic NOD mice (NOD-E), which do not develop clinical or histopathological symptoms of IDDM. This suggests that the observed **ductal** cell **proliferation** and differentiation was a direct result of beta-cell destruction and insulin insufficiency in these adult diabetic mice, which further suggests that these events are recapitulating islet ontogeny observed during embryogenesis. It is possible that comparable processes occur in the human diabetic **pancreas**.

L18 ANSWER 21 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 11
AN 1996:216872 BIOSIS
DN PREV199698773001
TI **PDX-1** is required for **pancreatic** outgrowth and differentiation of the rostral duodenum.
AU Offield, Martin F.; Jetton, Tom L.; Labosky, Patricia A.; Ray, Michael; Stein, Roland W.; Magnuson, Mark A.; Hogan, Brigid L.; Wright, Christopher V. E. (1)
CS (1) Dep. Cell Biol., Vanderbilt Univ. Sch. Med., 1161 21st Avenue South, Nashville, TN 37232-2175 USA
SO Development (Cambridge), (1996) Vol. 122, No. 3, pp. 983-995.
ISSN: 0950-1991.
DT Article
LA English
AB It has been proposed that the Xenopus homeobox gene, XlHbox8, is involved in endodermal differentiation during **pancreatic** and duodenal development (Wright, C. V. E., Schnegelsberg, P. and De Robertis, E. M. (1988). Development 105, 787-794). To test this hypothesis directly, gene targeting was used to make two different null mutations in the mouse XlHbox8 homolog,pdr-1. In the first, the second **pdx-1** exon, including the homeobox, was replaced by a neomycin resistance cassette. In the second, a lacZ reporter was fused in-frame with the N terminus of **PDX-1**, replacing most of the homeodomain.

Neonatal **pdx-1**-/mice are apancreatic, in confirmation of previous reports (Jonsson, J., Carlsson, L., Edlund, T. and Edlund, H. (1994). Nature 371, 606-609). However, the **pancreatic** buds do form in homozygous mutants, and the dorsal bud undergoes limited **proliferation** and outgrowth to form a small, irregularly branched, **ductular** tree. This outgrowth does not contain insulin or amylase-positive cells, but glucagon-expressing cells are found. The rostral duodenum shows a local absence of the normal columnar epithelial lining, villi, and Brunner's glands, which are replaced by a GLUT2-positive cuboidal epithelium resembling the bile **duct** lining. Just distal of the abnormal epithelium, the numbers of enteroendocrine cells in the villi are greatly reduced. The **PDX-1**/beta-galactosidase fusion allele is expressed in **pancreatic** and duodenal cells in the absence of functional **PDX-1**, with expression continuing into perinatal stages with similar boundaries and expression levels. These results offer additional insight into the role of **pdx-1** in the determination and differentiation of the posterior foregut, particularly regarding the **proliferation** and differentiation of the **pancreatic** progenitors.

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1	160	pdx-1 or idx-1 or ipf-1 or stf-1 or pdx1 or idx1 or ipf1 or stf1	USPAT; US-PGPUB; EPO; JPO; DEPWENT	2002/09/10 16:35
2	388	(424/1.49).CCLS.	USPAT; US-PGPUB; EPO; JPO; DEPWENT	2002/09/10 16:35
3	198	(424/9.34).CCLS.	USPAT; US-PGPUB; EPO; JPO; DEPWENT	2002/09/10 16:40
4	3933	(435/4).CCLS.	USPAT; US-PGPUB; EPO; JPO; DEPWENT	2002/09/10 16:40
5	1656	(435/7.21).CCLS.	USPAT; US-PGPUB; EPO; JPO; DEPWENT	2002/09/10 16:40
6	1397	(435/7.23).CCLS.	USPAT; US-PGPUB; EPO; JPO; DEPWENT	2002/09/10 16:40
7	205	(435/960).CCLS.	USPAT; US-PGPUB; EPO; JPO; DEPWENT	2002/09/10 16:40
8	7012	((424/1.49).CCLS.) or ((424/9.34).CCLS.) or ((435/4).CCLS.) or ((435/7.21).CCLS.) or ((435/7.23).CCLS.) or ((435/960).CCLS.)	USPAT; US-PGPUB; EPO; JPO; DEPWENT	2002/09/10 16:41
9	9	(pdx-1 or idx-1 or ipf-1 or stf-1 or pdx1 or idx1 or ipf1 or stf1) and (((424/1.49).CCLS.) or ((424/9.34).CCLS.) or ((435/4).CCLS.) or ((435/7.21).CCLS.) or ((435/7.23).CCLS.) or ((435/960).CCLS.))	USPAT; US-PGPUB; EPO; JPO; DEPWENT	2002/09/10 16:41

E26,779

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NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	EDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	BCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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FILE 'HOME' ENTERED AT 13:53:53 ON 10 SEP 2002

=> file biosis
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
                                                            0.21       0.21
FULL ESTIMATED COST

FILE 'BIOSIS' ENTERED AT 13:54:13 ON 10 SEP 2002
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 4 September 2002 (20020904/ED)


=> pdx(W)1
PDX(W)1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s pdx(W)1
            328 PDX
        2769592 1
L1          214 PDX(W)1

=> s Idx(W)1
            157 IDX
        2769592 1
L2           38 IDX(W)1

=> s Ipf(W)1
            665 IPF
              7 IPFS
            669 IPF
                  (IPF OR IPFS)
        2769592 1
L3           64 IPF(W)1

=> s stf(W)1
            254 STF
             24 STFS
            268 STF
                  (STF OR STFS)
        2769592 1
L4           45 STF(W)1

=> s pdx1
L5           81 PDX1

=> s idx1
L6            6 IDX1

=> s ipf1
L7           59 IPF1

=> s stf1
L8           13 STF1

=> s islet(W)duodenum(W)homeo?(W)protein(W)1
```

```
         19580 ISLET
         14865 ISLETS
         27897 ISLET
                 (ISLET OR ISLETS)
         16771 DUODENUM
            40 DUODENUMS
           116 DUODENA
         16849 DUODENUM
                 (DUODENUM OR DUODENUMS OR DUODENA)
        994369 HOMEO?
       1234078 PROTEIN
        464105 PROTEINS
       1423261 PROTEIN
                 (PROTEIN OR PROTEINS)
       2769592 1
L9            0 ISLET(W)DUODENUM(W)HOMEO?(W)PROTEIN(W)1

=> s insulin(W)promoter(W)factor(W)1
        196120 INSULIN
           991 INSULINS
        196904 INSULIN
                 (INSULIN OR INSULINS)
         93569 PROMOTER
         33024 PROMOTERS
        102945 PROMOTER
                 (PROMOTER OR PROMOTERS)
        666185 FACTOR
        498806 FACTORS
       1051474 FACTOR
                 (FACTOR OR FACTORS)
       2769592 1
L10           81 INSULIN(W)PROMOTER(W)FACTOR(W)1

=> s somatostatin(W)transcrip?(W)factor(W)1
         24819 SOMATOSTATIN
            95 SOMATOSTATINS
         24939 SOMATOSTATIN
                 (SOMATOSTATIN OR SOMATOSTATINS)
        272003 TRANSCRIP?
        666185 FACTOR
        498806 FACTORS
       1051474 FACTOR
                 (FACTOR OR FACTORS)
       2769592 1
L11           9 SOMATOSTATIN(W)TRANSCRIP?(W)FACTOR(W)1

=> s l1 or l2 or l3 or l4 or l5 or l6 or l7 or l8 or l9 or l10 or l11
L12         454 L1 OR L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11

=> s pancreat
6 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s pancreas?
L13      17[illegible] PANCREAS?

=> s duct
=> s duct?
L14       63670 DUCT?

=> s divid
=> s divid? or division or propagat? or proliferat? or mitotic? or mitosis
```

```
        111857 DIVID?
         45962 DIVISION
          9119 DIVISIONS
         52158 DIVISION
                 (DIVISION OR DIVISIONS)
         34208 PROPAGAT?
        215599 PROLIFERAT?
         34186 MITOTIC?
         23295 MITOSIS
          3790 MITOSES
         26106 MITOSIS
                 (MITOSIS OR MITOSES)
L15     434631 DIVID? OR DIVISION OR PROPAGAT? OR PROLIFERAT? OR MITOTIC? OR
               MITOSIS

=> s l12 and l13 and l14 and l15
L16          16 L12 AND L13 AND L14 AND L15

=> save temp
ENTER L#, L# RANGE, ALL, OR (END):l16
ENTER NAME OR (END):idx1/a
ANSWER SET L16 HAS BEEN SAVED AS 'IDX1/A'

=> file ca
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY     SESSION
FULL ESTIMATED COST                                   18.26       18.47

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FILE COVERS 1907 - 5 Sep 2002 VOL 137 ISS 11
FILE LAST UPDATED: 5 Sep 2002  (20020905/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

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information on CAS roles, enter HELP ROLES at an arrow prompt or use
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=> s l15
           695 PLA
       7055386 L
           157 PLA(W)L
           117 IDX
       7055386 L
            35 IDX(W)L
           351 IPF
            11 IPFS
```

```
    356 IPF
          (IPF OR IPFS)
7055386 1
     59 IPF(W)1
    350 STF
     41 STFS
    375 STF
          (STF OR STFS)
7055386 1
     46 STF(W)1
    149 PDX1
     19 IDX1
     80 IPF1
     34 STF1
  20070 ISLET
  11986 ISLETS
  22753 ISLET
          (ISLET OR ISLETS)
  15382 DUODENUM
     48 DUODENUMS
     [illegible] DUODENA
  15431 DUODENUM
          (DUODENUM OR DUODENUMS OR DUODENA)
  34769 HOMEO?
1397970 PROTEIN
 925628 PROTEINS
1612137 PROTEIN
          (PROTEIN OR PROTEINS)
7055386 1
      0 ISLET(W)DUODENUM(W)HOMEO?(W)PROTEIN(W)1
  13981 INSULIN
   5107 INSULINS
 139917 INSULIN
          (INSULIN OR INSULINS)
 121439 PROMOTER
  47111 PROMOTERS
 132090 PROMOTER
          (PROMOTER OR PROMOTERS)
 710782 FACTOR
 616573 FACTORS
1122846 FACTOR
          (FACTOR OR FACTORS)
7055386 1
     92 INSULIN(W)PROMOTER(W)FACTOR(W)1
  16148 SOMATOSTATIN
    129 SOMATOSTATINS
  16154 SOMATOSTATIN
          (SOMATOSTATIN OR SOMATOSTATINS)
 267101 TRANSCRIP?
 710782 FACTOR
 616573 FACTORS
1122846 FACTOR
          (FACTOR OR FACTORS)
7055386 1
      8 SOMATOSTATIN(W)TRANSCRIP?(W)FACTOR(W)1
  64427 PANCREA?
  41483 DUCT
 110007 DIVID?
  15493 DIVISION
   5089 DIVISIONS
  59464 DIVISION
          (DIVISION OR DIVISIONS)
 128410 PROLIFERAT?
 154870 PROLIFERAT?
```

```
        23240 MITOTIC?
        24306 MITOSIS
         1922 MITOSES
        25365 MITOSIS
                (MITOSIS OR MITOSES)
L17        16 L12 AND L13 AND L14 AND L15

=> duplicate rem
ENTER L# LIST OR (END):l16-l17
DUPLICATE PREFERENCE IS 'BIOSIS, CA'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
                                                         51.53      70.00
FULL ESTIMATED COST

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PROCESSING COMPLETED FOR L16
PROCESSING COMPLETED FOR L17
L18           21 DUPLICATE REM L16-L17 (11 DUPLICATES REMOVED)

=> d l18 1-21 bib ab

L18  ANSWER 1 OF 21  CA  COPYRIGHT 2002 ACS
AN   136:121238  CA
TI   Bile duct progenitor cells and methods of use
IN   Pang, Kevin; Homa, Monica
PA   USA
SO   U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Ser. No. 973,938.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.         KIND  DATE          APPLICATION NO.   DATE
     ---------------    ----  --------      ---------------   --------
PI   US 2002012653      A1    20020131      US 1997-994539    19971219
     WO 9640872         A1    19961219      WO 1996-US9656    19960607
         W:  AU, CA, JP, KR, US
         RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRAI WO 1996-US9656     W     19960607
     US 1998-973938     A2    19980821
     US 1995-478064     A     19950607
AB   The present invention relates to a substantially pure population of viable
     bile duct progenitor cells, and methods for isolating such
     cells. The present invention further concerns certain therapeutic uses
     for such progenitor cells, and their progeny.

L18  ANSWER 2 OF 21  CA  COPYRIGHT 2002 ACS
AN   135:24733  CA
TI   Pancreatic stem cells and their use in transplantation
IN   Abraham, Elizabeth J.; Faustman, Denise; Habener, Joel L.; Vallejo, Mario;
     Zulewski, Hendrik
PA   General Hospital Corporation, USA
SO   PCT Int. Appl., 102 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE          APPLICATION NO.   DATE
```

PI	WO 2001039784	A1	20010607	WO 2000-US33031	20001206

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	US 2001024824	A1	20010927	US 2000-731255	20001206
	US 2001046489	A1	20011129	US 2000-731261	20001206
PRAI	US 1999-169082P	P	19991206		
	US 2000-215109P	P	20000628		
	US 2000-238880P	P	20001006		

AB Methods and compns. are described for the treatment of type I insulin-dependent diabetes mellitus and other conditions in a patient using newly identified stem cells that are capable of differentiation into a variety of **pancreatic** islet cells, including insulin-producing beta cells, as well as hepatocytes. Addnl., the patient may be treated with an immunosuppressant agent. Nestin has been identified as a mol. marker for **pancreatic** stem cells, while cytokeratin-19 serves as a marker for a distinct class of islet **ductal** cells. Methods are described whereby nestin-pos. stem cells can be isolated from **pancreatic** islets and cultured to obtain further stem cells or pseudo-islet like structures. Methods for ex vivo differentiation of the **pancreatic** stem cells are disclosed. Methods are described whereby **pancreatic** stem cells can be isolated, expanded, and transplanted into a patient in need thereof, either allogeneically, isogeneically or xenogenically, to provide replacement for lost or damaged insulin-secreting cells or other cells. For example, a 3-fold stimulation of nestin mRNA levels in the islets cultured in high glucose compared to the islets cultured in normal glucose was obsd. Similarly, injection of glucagon-like peptide 1 (GLP-1) into mice was found to increase islet mass by 2-fold in 48 h.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1

AN 2002:280266 BIOSIS

DN PREV200200280266

TI **Pancreatic** duodenal homeobox-1, **PDX-1**, a major regulator of beta cell identity and function.

AU McKinnon, C. M.; Docherty, K. (1)

CS (1) Department of Molecular and Cell Biology, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD: k.docherty@aberdeen.ac.uk UK

SO Diabetologia, (October, 2001) Vol. 44, No. 10, pp. 1203-1214. print. ISSN: 0012-186X.

DT General Review

LA English

AB **Pancreatic** duodenal homeobox -1 is a transcription factor that is expressed in beta and delta cells of the islets of Langerhans and in dispersed endocrine cells of the duodenum. It is involved in regulating the expression of a number of key beta-cell genes as well as somatostatin. It also plays a pivotal part in the development of the **pancreas** and islet cell ontogeny. Thus homozygous disruption of the gene in mice and humans results in **pancreatic** agenesis. Heterozygous mutations in the gene result in impaired glucose tolerance and symptoms of diabetes as seen in MODY4 and late-onset Type II (non-insulin-dependent) diabetes mellitus. In adults **pancreatic** duodenal homeobox-1 expression is increased in **duct** cells of the **pancreas**

that have been induced to **proliferate** and differentiate to form new islets. Defects in **pancreatic** duodenal homeobox-1 could therefore contribute to Type II diabetes by affecting compensatory mechanisms that increase the rate of beta-cell neogenesis to meet the increased insulin secretory demand. It could also be a pharmacological target for beta-cell defects in Type II diabetes, while its role as a regulator of islet stem cell activity is being exploited to produce a replenishable source of islet tissue for transplantation in Type I (insulin-dependent) diabetes mellitus.

L18 ANSWER 4 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 2001:142229 BIOSIS
DN PREV200100142229
TI PDX:PBX complexes are required for normal **proliferation** of **pancreatic** cells during development.
AU Dutta, Sanjoy; Gannon, Maureen; Peers, Bernard; Wright, Chris; Bonner-Weir, Susan; Montminy, Marc (1)
CS (1) Clayton Laboratories for Peptide Biology, Salk Institute, 10010 North Torrey Pines Road, La Jolla, CA, 92037: montminy@salk.edu USA
SO Proceedings of the National Academy of Sciences of the United States of America (January 30, 2001) Vol. 98, No. 3, pg. 1065-1070. print. ISSN: 0027-8424.
DT Article
LA English
SL English
AB The homeobox factor **PDX-1** is a key regulator of **pancreatic** morphogenesis and glucose homeostasis; targeted disruption of the **PDX-1** gene leads to **pancreatic** agenesis in **pdx-1**(-/-) homozygotes. **Pdx-1** heterozygotes develop normally, but they display glucose intolerance in adulthood. Like certain other homeobox proteins, **PDX-1** contains a consensus FPWMK motif that promotes heterodimer formation with the ubiquitous homeodomain protein PBX. To evaluate the importance of **PDX-1**:PBX complexes in **pancreatic** morphogenesis and glucose homeostasis, we expressed either wild-type or PBX interaction defective **PDX-1** transgenes under control of the **PDX-1** promoter. Both wild-type and mutant **PDX-1** transgenes corrected glucose intolerance in **pdx-1** heterozygotes. The wild-type **PDX-1** transgene rescued the development of all **pancreatic** lineages in **pdx-1**(-/-) animals, and these mice survived to adulthood. In contrast, **pancreata** from **pdx-1**(-/-) mice expressing the mutant **PDX-1** transgene were hypoplastic, and these mice died within 3 weeks of birth from **pancreatic** insufficiency. All **pancreatic** cell types were observed in **pdx-1**(-/-) mice expressing the mutant **PDX-1** transgene; but the islets were smaller, and increased numbers of islet hormone-positive cells were noted within the **ductal** epithelium. These results indicate that **PDX-1**:PBX complexes are dispensable for glucose homeostasis and for differentiation of stem cells into **ductal**, endocrine, and acinar lineages; but they are essential for expansion of these populations during development.

L18 ANSWER 5 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 2001:74765 BIOSIS
DN PREV200100214765
TI Multipotential nestin-positive stem cells isolated from adult **pancreatic** islets differentiate ex vivo into **pancreatic** endocrine, exocrine, and hepatic phenotypes.
AU Zulewski, Henryk; Abraham, Elizabeth J.; Gerlach, Melissa J.; Daniel, Philip B.; Moritz, Wolfgang; Muller, Beat; Vallejo, Mario; Thomas, Melissa

K.; Habener, Joel F. (1)
CS (1) Laboratory of Molecular Endocrinology, Massachusetts General Hospital, 55 Fruit St., WEL320, Boston, MA, 02114: jhabener@partners.org USA
SO Diabetes, (March, 2001) Vol. 50, No. 3, pp. 521-533. print.
ISSN: 0012-1797.
DT Article
LA English
SL English
AB The endocrine cells of the rat **pancreatic** islets of Langerhans, including insulin-producing beta-cells, turn over every 40-50 days by processes of apoptosis and the **proliferation** and differentiation of new islet cells (neo-genesis) from progenitor epithelial cells located in the **pancreatic ducts**. However, the administration to rats of islet trophic factors such as glucose or glucagon-like peptide 1 for 48 h results in a doubling of islet cell mass, suggesting that islet progenitor cells may reside within the islets themselves. Here we show that rat and human **pancreatic** islets contain a heretofore unrecognized distinct population of cells that express the neural stem cell-specific marker nestin. Nestin-positive cells within **pancreatic** islets express neither the hormones insulin, glucagon, somatostatin, or **pancreatic** polypeptide nor the markers of vascular endothelium or neurons, such as collagen IV and galanin. Focal regions of nestin-positive cells are also identified in large, small, and centrolobular **ducts** of the rat **pancreas**. Nestin-positive cells in the islets and in **pancreatic ducts** are distinct from **ductal** epithelium because they do not express the **ductal** marker cytokeratin 19 (CK19). After their isolation, these nestin-positive cells have an unusually extended **proliferative** capacity when cultured in vitro (apprx8 months), can be cloned repeatedly, and appear to be multipotential. Upon confluence, they are able to differentiate into cells that express liver and exocrine **pancreas** markers, such as alpha-fetoprotein and **pancreatic** amylase, and display a **ductal**/endocrine phenotype with expression of CK19, neural-specific cell adhesion molecule, insulin, glucagon, and the **pancreas**/duodenum specific homeodomain transcription factor, **IDX-1**. We propose that these nestin-positive islet-derived progenitor (NIP) cells are a distinct population of cells that reside within **pancreatic** islets and may participate in the neogenesis of islet endocrine cells. The NIP cells that also reside in the **pancreatic ducts** may be contributors to the established location of islet progenitor cells. The identification of NIP cells within the **pancreatic** islets themselves suggest possibilities for treatment of diabetes, whereby NIP cells isolated from **pancreas** biopsies could be expanded ex vivo and transplanted into the donor/recipient.

L18 ANSWER 6 OF 21 CA COPYRIGHT 2002 ACS
AN 133:38709 CA
TI An animal model for identifying a common stem/progenitor to liver cells and **pancreatic** cells
IN Sarvetnick, Nora; Krakowski, Michelle L.; Kritzik, Marcie R.
PA The Scripps Research Institute, USA
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000036091	A2	20000622	WO 1999-US29490	19991213
	WO 2000036091	A3	20001109		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,

MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1141247 A2 20011010 EP 1999-967280 19991213
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

US 2001013134 A1 20010809 US 2001-826779 20010405

PRAI US 1998-212531 A2 19981216
WO 1999-US29490 W 19991213

AB The invention provides animal models, where the ectopic expression of KGF, EGF, or both is under the control of a **pancreas**-specific promoter, e.g., the insulin promoter. The expression of KGF in the ins-KGF **pancreatic** islets of Langerhans results in enlarged islets, with substantial **proliferation** of **duct** cells within the islet mass, and the presence of albumin and alpha-fetoprotein-producing hepatocytes in the islets of the ins-KGF **pancreata**. The compns. and methods disclosed are useful for identifying and isolating **pancreatic** stem/progenitor cells, including a common stem/progenitor to liver cells and **pancreatic** cells.

L18 ANSWER 7 OF 21 CA COPYRIGHT 2002 ACS
AN 135:301720 CA
TI Human **pancreatic** stem cell and diabetes cell therapy
AU Pattou, Francois; Kerr-Conte, Julie; Gmyr, Valery; Vandewalle, Brigitte; Vantyghem, Marie-Christine; Lecomte-Houcke, Martine; Proye, Charles; Lefebvre, Jean
CS Hospitalo-Universitaire, UPRES 1048 de Universite de Lille 2 et Service de Chirurgie Generale et Endocrinienne, Centre Hospitalier, Universitaire de Lille, Lille, F59037, Fr.
SO Bulletin de l'Academie Nationale de Medecine (Paris, France) (2000), 184(9), 1887-1901
CODEN: BANMAC; ISSN: 0001-4079
PB Academie Nationale de Medecine
DT Journal, General Review
LA French
AB A review, with refs. Cell therapy offers today important perspectives for the treatment of type 1 diabetes. The current utilization of primary human islets of Langerhans nevertheless forbids all hope of developing this treatment on a large scale. The recent description of the persistence of stem cells capable of **proliferating** and differentiating in the adult **pancreas** offers an attractive alternative for the prodn. in vitro of homologous insulin-secreting cells. We first reproduced in vitro from human islet prepns. the **proliferation** of **ductal** epithelial structures and their progressive organization. Thereafter, we focused on the description of a reproducible source of human **ductal** cells by the transdifferentiation of exocrine prepns. More recently we described in these exocrine derived **ductal** cells the expression the of **insulin promoter factor-1** (**IPF-1**/otherwise known as **PDX-1**), a transcription factor essential for the differentiation of **ductal** cells into endocrine cells during both development and **pancreatic** regeneration. If the **proliferation** and differentiation of these cells is confirmed, this approach could lead to the description of an abundant source of human **pancreatic** stem cells for the prodn. ex vivo of human insulin secreting cells and may even allow autologous cell therapy, in the absence of immunosuppression.
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 8 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
AN 2001:267534 BIOSIS
DN PREV200100267534
TI Adult human cytokeratin 19-positive cells reexpress **insulin promoter factor 1** in vitro: Further evidence for pluripotent **pancreatic** stem cells in humans.
AU Gmyr, Valery; Kerr-Conte, Julie (1); Belaich, Sandrine; Vandewalle, Brigitte; Leteurtre, Emmanuelle; Vantyghem, Marie Christine; Lecomte-Houcke, Martine; Proye, Charles; Lefebvre, Jean; Pattou, Francois
CS (1) Laboratory of Cell Culture, University Hospital Center of Lille, 1 Place de Verdun, Lille, 59045: jkerr-conte@univ-lille2.fr France
SO Diabetes, (October, 2000) Vol. 49, No. 10, pp. 1671-1680. print. ISSN: 0012-1797.
DT Article
LA English
SL English
AB Human **pancreatic** cells with a typical **ductal** phenotype and potential to **proliferate** can be obtained in vitro, but the differentiation capacity of these putative human **pancreatic** stem cells remains to be documented. We investigated the protein and mRNA expression of **insulin promoter factor 1** (**IPF-1**) (or **pancreas**/duodenal homeobox 1), a transcription factor critical for **pancreatic** development and endocrine cell neogenesis, in human **pancreatic** **ductal** cells derived from cultured exocrine tissue. In vitro, exocrine cells rapidly adhered (within 12 h) and were de-/transdifferentiated to **ductal** cells after 3 days with a dramatic loss of amylase protein (n = 4, 92 +- 3.3%, P < 0.05 vs. day 1) and a simultaneous increase of **ductal** cytokeratin 19 protein (n = 4, 3.4-fold on day 3 and 7-fold on day 9, P < 0.05 vs. day 1). **IPF-1** protein and mRNA levels were low to undetectable in exocrine preparations before culture. After 2 days of culture, a 3.2-fold increase in **IPF-1** protein was observed, corresponding to the characteristic 46-kDa protein in Western blots. Reverse transcriptase-polymerase chain reaction confirmed a 10.5-fold increase in **IPF-1** mRNA levels after 3 days of culture (n = 5, P < 0.001 vs. day 1). Double immunocytochemistry showed direct evidence that **IPF-1** appeared during culture in these exocrine-derived **ductal** cells (cytokeratin 7-positive) and was not merely in contaminating endocrine cells (chromogranin A-positive). In conclusion, we describe herein the first converging evidence on both the molecular and protein level that human cells with a typical **ductal** phenotype derived ex vivo from **pancreatic** exocrine tissue (obtained from healthy donors) can reexpress **IPF-1** in culture, suggesting their **pancreatic** precursor/stem cell potential.

L18 ANSWER 9 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
AN 2000:377198 BIOSIS
DN PREV200000377198
TI Modulation of rat **pancreatic** acinoductal transdifferentiation and expression of **PDX-1** in vitro.
AU Rooman, I.; Heremans, Y.; Heimberg, H.; Bouwens, L. (1)
CS (1) Department of Experimental Pathology, VUB, Laarbeeklaan 103, B-1090, Brussels Belgium
SO Diabetologia, (July, 2000) Vol. 43, No. 7, pp. 907-914. print. ISSN: 0012-186X.
DT Article
LA English
SL English
AB Aims/hypothesis. In adult **pancreatic** regeneration models exocrine acini are found to transdifferentiate to **duct**-like

complexes. This has also been associated with the formation of new endocrine islet cells. We aimed to establish an in vitro model in which this transdifferentiation process is characterised and can be modulated. Methods: Purified rat **pancreatic** acini were cultured in suspension. Differentiation was analysed by immunocytochemistry, electron microscopy, western blotting and RT-PCR. Results: During culture acinar cells directly transdifferentiated without **dividing**, the cells lost their acinar phenotype and started to express cytokeratins 20 and 7 and fetal liver kinase-1 (Flk-1) receptors for vascular endothelial growth factor. Expression of the acinar **pancreatic** exocrine transcription factor (PTF-1) remained and the **pancreatic** duodenal homeobox-containing transcription factor (**PDX-1**) was induced. When transdifferentiation was completed, the cells started to express protein gene product 9.5, a panneuroendocrine marker. By combining these features, the transdifferentiated cells show similar characteristics to precursor cells during active beta-cell neogenesis. We were able to modulate the differentiation state by addition of nicotinamide or sodium butyrate, agents which are known to stimulate endocrine differentiation in other models. Conclusion/interpretation: Here, we present an in vitro system in which the cellular differentiation of putative **pancreatic** endocrine precursor cells and their **PDX 1** expression can be modulated, thereby providing a possible model for the study of beta-cell transdifferentiation.

L18 ANSWER 10 OF 21 CA COPYRIGHT 2002 ACS
AN 133:84532 CA
TI Insulinotropic glucagon-like peptide 1 agonists stimulate expression of homeodomain protein **IDX-1** and increase islet size in mouse **pancreas**
AU Stoffers, Doris A.; Kieffer, Timothy J.; Hussain, Mehboob A.; Drucker, Daniel J.; Bonner-Weir, Susan; Habener, Joel F.; Egan, Josephine M.
CS Division of Endocrinology, Diabetes and Metabolism, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
SO Diabetes (2000), 49(5), 741-748
CODEN: DIAEAN; ISSN: 0012-1797
PB American Diabetes Association
DT Journal
LA English
AB Diabetes is caused by a failure of the **pancreas** to produce insulin in amts. sufficient to meet the body's needs. A hallmark of diabetes is an abs. (type 1) or relative (type 2) redn. in the mass of **pancreatic** .beta.-cells that produce insulin. Mature .beta.-cells have a life-span of apprx.48-56 days (rat) and are replaced by the replication of preexisting .beta.-cells and by the differentiation and **proliferation** of new .beta.-cells (neogenesis) derived from the **pancreatic ducts**. The insulinotropic hormone glucagon-like peptide (GLP)-1, which is produced by the intestine, enhances the **pancreatic** expression of the homeodomain transcription factor **IDX-1** that is crit. for **pancreas** development and the transcriptional regulation of the insulin gene. Concomitantly, GLP-1 administered to diabetic mice stimulates insulin secretion and effectively lowers their blood sugar levels. GLP-1 also enhances beta.-cell neogenesis and islet size. Thus, in addn. to stimulating insulin secretion, GLP-1 stimulates the expression of the transcription factor **IDX-1** while stimulating .beta.-cell neogenesis and may thereby be an effective treatment for diabetes.
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 11 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:38563 BIOSIS
DN PREV200100038563
TI Hydrolysed casein diet protects BB rats from developing diabetes by

promoting islet neogenesis.

AU Wang, Gen-Sheng; Gruber, Heidi; Smyth, Peter; Pulido, Olga; Rosenberg, Lawrence; Duguid, William; Scott, Fraser W. (1)

CS (1) Laboratory N1, Ottawa Hospital Research Institute, Ottawa Hospital-General Campus, 501 Smyth Road, Ottawa, ON, K1H 8L6: fscott@ottawahospital.on.ca Canada

SO Journal of Autoimmunity, (Dec., 2000) Vol. 15, No. 4, pp 407-416. print. ISSN: 0896-8411.

DT Article

LA English

SL English

AB Feeding diabetes-prone BioBreeding (BBdp) rats a hydrolysed-casein (HC)-based semi-purified diet results in two-to-three-fold fewer diabetes cases compared with feeding cereal-based diets such as NIH-07 (NIH). We showed previously that young NIH-fed BBdp rats had decreased islet area at a time when classic insulitis was minimal. Rats fed an HC diet maintained near normal islet area followed 3-4 weeks later by a deviation of the **pancreas** cytokine pattern from Th1 to Th2/Th3. This finding raised the possibility that BBdp rats were more susceptible to diet-induced changes in islet homeostasis. To investigate this possibility further, BBdp rats were fed an NIH or HC diet from days 23 to 45. Bouin's fixed sections of **pancreas** were stained with H & E or antibodies for insulin and glucagon. Cell **proliferation** nuclear antigen (PCNA) was used as a marker of cell **proliferation** and cells were stained for putative markers of islet neogenesis, cytokeratin 20 (CK20) and Bcl-2. Apoptotic bodies were recognized by morphological features and by TUNEL-positive staining. BBdp rats fed an HC diet had a significantly higher beta-cell fraction than rats fed NIH, whereas alpha-cell fraction and beta-cell size were not affected by diet or rat type. Apoptotic bodies of beta-cells were rare and unaffected by diet. The number of PCNA+ beta-cells was not affected by diet. CK20 expression was localized in the **ductular** system and at the periphery of islets in rats aged 7 and 45 days. There were more CK20+ islets in BBdp rats fed NIH than in those fed HC but the CK20 area fraction was unaffected by diet. Bcl-2 expression was scattered among **ducts** and central acinar cells. The number of extra-islet insulin+ and glucagon+ clusters (<four cells) was significantly higher in animals fed the HC diet compared with those fed NIH. Most of the insulin+ clusters were also homeodomain-containing transcription factor **pancreas** duodenum homeobox gene-1 (**PDX-1**) positive. Glucagon+/**PDX-1**+ clusters were rarely found. These data are consistent with a shift in **pancreas** homeostasis that maintains islet cell mass by increased islet neogenesis, a process that was enhanced in animals fed a diabetes-retardant diet.

L18 ANSWER 12 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6

AN 2000:216835 BIOSIS

DN PREV200000216835

TI Diabetes and **pancreatic** tumours in transgenic mice expressing Pa X 6.

AU Yamaoka, T. (1); Yano, M.; Yamada, T.; Matsushita, T.; Moritani, M.; Ii, S.; Yoshimoto, K.; Hata, J.; Itakura, M.

CS (1) Otsuka Department of Molecular Nutrition, School of Medicine, University of Tokushima, Tokushima, 770-8503 Japan

SO Diabetologia, (March, 2000) Vol. 43, No. 3, pp. 332-339. ISSN: 0012-186X.

DT Article

LA English

SL English

AB Aims/hypothesis: Both endocrine and exocrine cells of the **pancreas** differentiate from epithelial cells of primitive **pancreatic** **ducts**, and four types of **pancreatic** islet cells (alpha, beta, delta, and PP cells) are derived from the common pluripotent

precursor cells. Although Pa X 6 is expressed in all islet cells, Pa X 4 is detected only in beta cells. In homozygous Pa X 4-null mice, beta cells are absent, whereas the number of alpha cells is increased. Therefore, we hypothesized that the balance of Pa X 4 and 6 is one of the determinants by which the common progenitor cells differentiate into alpha or beta cells. Methods: To change this balance, we generated transgenic mice overexpressing Pa X 6 driven by the insulin promoter or the **PDX1** promoter. Results: In both types of transgenic mice, normal development of beta cells was disturbed, resulting in apoptosis of beta cells and diabetes. In Insulin/Pa X 6-Tg mice, beta cells were specifically affected, whereas in PDX/Pa X 6-Tg mice, developmental abnormalities involved the whole **pancreas** including hypoplasia of the exocrine **pancreas**. Furthermore, PDX/Pa X 6-Tg mice experienced **proliferation** of both **ductal** epithelia and islet cells and subsequent cystic adenoma of the **pancreas**. Conclusion/interpretation: These findings suggest that Pa X 6 promotes the growth of **ductal** epithelia and endocrine progenitor cells and that the suppression of Pa X 6 is necessary for the normal development of beta cells and the exocrine **pancreas**.

L18 ANSWER 13 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:59802 BIOSIS
DN PREV200000059802
TI Expansion of **Pdx1**-expressing **pancreatic** epithelium and islet neogenesis in transgenic mice overexpressing transforming growth factor alpha.
AU Song, Si Young; Gannon, Maureen; Washington, M. K.; Scoggins, Charles R.; Meszoely, Ingrid M.; Goldenring, James R.; Marino, Christopher R.; Sandgren, Eric P.; Coffey, Robert J., Jr.; Wright, Christopher V. E.; Leach, Steven D. (1)
CS (1) Division of Surgical Oncology, T-2104 Medical Center North, Vanderbilt University Medical Center, 21st and Garland Streets, Nashville, TN USA
SO Gastroenterology, (Dec., 1999) Vol. 117, No. 6, pp. 1416-1426. ISSN: 0016-5085.
DT Article
LA English
SL English
AB Background & Aims: The progenitor cells responsible for transforming growth factor (TGF)-alpha-induced **pancreatic ductal** metaplasia and neoplasia remain uncharacterized. During **pancreatic** development, differentiated cell types arise from **ductal** progenitor cells expressing the **Pdx1** homeodomain transcription factor. The aims of this study were, first, to evaluate the role of **Pdx1**-expressing stem cells in MT-TGFalpha transgenic mice, and second, to further characterize cell **proliferation** and differentiation in this model. Methods: To assess **Pdx1** gene expression in normal and metaplastic epithelium, we performed in vivo reporter gene analysis using heterozygous Pdx1lacZ/+ and bigenic Pdx1lacZ/+/MT-TGFalpha mice. Results: Pdx1lacZ/+/MT-TGFalpha bigenics showed up-regulated **Pdx1** expression in premalignant metaplastic **ductal** epithelium. In addition to **Pdx1** gene activation, TGF-alpha-induced metaplastic epithelium demonstrated a pluripotent differentiation capacity, as evidenced by focal expression of Pax6 and initiation of islet cell neogenesis. The majority of **Pdx1**-positive epithelial cells showed no expression of insulin, similar to the pattern observed during embryonic development. Conclusions: Overexpression of TGF-alpha induces expansion of a **Pdx1**-expressing epithelium characterized by focal expression of Pax6 and initiation of islet neogenesis. These findings suggest that premalignant events induced by TGF-alpha in mouse **pancreas** may recapitulate a developmental program active during embryogenesis.

L18 ANSWER 14 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:324535 BIOSIS

DN PREV199900324535
TI Activation of the **Pdx1** homeobox gene during TGFa-induced premalignant **pancreatic ductal proliferation** : In vivo reporter gene analysis using "double transgenic" mice.
AU Song, Si Young (1); Gannon, Maureen (1); Meszoely, Ingrid M. (1); Scoggins, Charles R. (1); Yang, LiYing (1); Wright, Christopher V. E. (1); Coffey, Robert J. (1); Leach, S. D.
CS (1) Vanderbilt Univ Med Ctr, Nashville, TN USA
SO Gastroenterology, (April, 1999) Vol. 116, No. 4 PART 2, pp. A1164. Meeting Info.: Digestive Disease Week and the 100th Annual Meeting of the American Gastroenterological Association Orlando, Florida, USA May 16-19, 1999 American Gastroenterological Association . ISSN: 0016-5085.
DT Conference
LA English

L18 ANSWER 15 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:293778 BIOSIS
DN PREV199900293778
TI Sustained **proliferation** of **PDX-1**+ cells derived from human islets.
AU Beattie, Gillian M.; Itkin-Ansari, Pamela; Cirulli, Vincenzo; Leibowitz, Gil; Lopez, Ana D.; Bossie, Stuart; Mally, Martin I.; Levine, Fred; Hayek, Alberto (1)
CS (1) Islet Research Laboratory, Department of Pediatrics, UCSD, 9894 Genesee Ave., La Jolla, CA, 92037 USA
SO Diabetes, (May, 1999) Vol. 48, No. 5, pp. 1013-1019. ISSN: 0012-1797.
DT Article
LA English
SL English
AB Ex vivo expansion of human beta-cells is an important step toward the development of cell-based insulin delivery systems in type 1 diabetes. Here, we report that human **pancreatic** endocrine cells can be expanded through 15 cell doublings in vitro for an estimated total 30,000-fold increase in cell number. We believe that the cells resulting from these cultures are of beta-cell origin, since they uniformly express the transcription factor **PDX-1** (**STF-1**, **IDX-1**, **IPF-1**), which is initially seen only in cells positive for insulin and negative for the **ductal** cell marker cytokeratin (CK)-19. To rule out the possibility that **PDX-1** expression might be induced by the culture conditions used here, cells from isolated human **pancreatic ducts** were cultured under the same conditions as the islet cells. Cells in these cultures expressed CK-19 but not **PDX-1**. Although the expanded beta-cells continued to express **PDX-1**, insulin expression was lost over time. Whether reexpression of islet-specific genes in vitro is essential for successful cell transplantation remains to be determined.

L18 ANSWER 16 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7
AN 2000:95419 BIOSIS
DN PREV200000095419
TI **PDX-1** and Msx-2 expression in the regenerating and developing **pancreas**.
AU Kritzik, M. R.; Jonas, R.; Chen, Z.; Krakowski, M., Krahl, T., Good, A.; Wright, C.; Fox, H.; Sarvetnick, N. (1)
CS (1) Department of Immunology, Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA, 92037 USA
SO Journal of Endocrinology, (Dec., 1999) Vol. 163, No. 3, pp. 523-530. ISSN: 0022-0795.
DT Article
LA English

SL English
AB We have observed **pancreatic duct** cell **proliferation** and islet regeneration in transgenic mice whose **pancreata** produce interferon gamma (IFNg mice). We have previously demonstrated that new islet cells derive from endocrine progenitor cells in the **pancreatic ducts** of this model. The current study was initiated to define these endocrine progenitor cells further and to identify novel markers associated with **pancreatic** regeneration. Importantly, we have found that **PDX-1**, a transcription factor required for insulin gene transcription as well as for **pancreatic** development during embryogenesis, is expressed in the **duct** cells of IFNg mice. This striking observation suggests an important role for **PDX-1** in the marked regeneration observed in IFNg mice, paralleling its critical function during ontogeny. Also demonstrated was elevated expression of the homeobox-containing protein Msx-2 in the **pancreata** of fetal mice as well as in adult IFNg mice, identifying this molecule as a novel marker associated with **pancreatic** development and regeneration as well. The identification of **PDX-1** and Msx in the **ducts** of the IFNg transgenic **pancreas** but not in the **ducts** of the non-transgenic **pancreas** suggests that these molecules are associated with endocrine precursor cells in the **ducts** of the IFNg transgenic mouse.

L18 ANSWER 17 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 8
AN 1999:153690 BIOSIS
DN PREV199900153690
TI The homeodomain protein **IDX-1** increases after an early burst of **proliferation** during **pancreatic** regeneration.
AU Sharma, Arun; Zangen, David H.; Reitz, Petra; Taneja, Monica; Lissauer, Matthew E.; Miller, Christopher P.; Weir, Gordon C.; Habener, Joel F.; Bonner-Weir, Susan (1)
CS (1) Joslin Diabetes Cent., One Joslin Pl., Boston, MA 02215 USA
SO Diabetes, (March, 1999) Vol. 48, No. 3, pp. 507-513.
ISSN: 0012-1797.
DT Article
LA English
AB Islet duodenal homeobox 1 (**IDX-1/IPF-1/STF-1/PDX-1**), a homeodomain protein that transactivates the insulin promoter, has been shown by targeted gene ablation to be required for **pancreatic** development. After 90% **pancreatectomy** (Px), the adult **pancreas** regenerates in a process recapitulating embryonic development, starting with a burst of **proliferation** in the epithelium of the common **pancreatic duct**. In this model, **IDX-1** mRNA was detected by semiquantitative reverse transcription-polymerase chain reaction in total RNA from isolated common **pancreatic ducts** at levels 10% of those of isolated islets. The **IDX-1** mRNA levels were not significantly different for common **pancreatic ducts** of Px, sham Px, and unoperated rats and did not change with time after surgery. By immunoblot analysis, **IDX-1** protein was only faintly detected in these **ducts** 1 and 7 days after Px or sham Px but was easily detected at 2 and 3 days after Px. Similarly, **IDX 1** immunostaining was barely detectable in sham or unoperated **ducts** but was strong in **ducts** at 2 3 days after Px. The increase of **IDX-1** immunostaining followed that of BrdU incorporation (**proliferation**). These results indicate a posttranscriptional regulation of the **IDX-1** expression in **ducts**. In addition, islets isolated 3-7 d after Px showed higher **IDX-1** protein expression than control islets. Thus, in **pancreatic** regeneration **IDX-1** is upregulated in newly **divided ductal** cells

as well as in islets. The timing of enhanced expression of **IDX-1** implies that **IDX-1** is not important in the initiation of regeneration but may be involved in the differentiation of **ductal** cells to beta-cells.

L18 ANSWER 18 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:289195 BIOSIS
DN PREV199900289195
TI Ontogeny of peptide growth factor and transcription factor expression during induced islet cell neogenesis in the neonatal rat **pancreas**.
AU Arany, E. (1); Strutt, B.; Duvillie, B.; Hill, D. J.
CS (1) Lawson Research Institute, St Joseph's Health Centre, University of Western Ontario, London, Ontario, N6A 4V2 Canada
SO Journal of Endocrinology, (March, 1999) Vol. 160, No. SUPPL., pp. P124. Meeting Info.: 18th Joint Meeting of the British Endocrine Societies Bournemouth, England, UK April 12-15, 1999 British Endocrine Societies . ISSN: 0022-0795.
DT Conference
LA English

L18 ANSWER 19 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 9
AN 1997:390039 BIOSIS
DN PREV199799689242
TI Demonstration of two different processes of beta-cell regeneration in a new diabetic mouse model induced by selective perfusion of alloxan.
AU Waguri, Masako (1); Yamamoto, Koji; Miyagawa, Jun-Ichiro; Tochino, Yoshihiro; Yamamori, Katsumi; Kajimoto, Yoshitaka; Nakajima, Hiromu; Watada, Hirotaka; Yoshiuchi, Issei; Itoh, Naoto; Imagawa, Akihisa; Namba, Mitsuyoshi; Kuwajima, Masamichi; Yamasaki, Yoshimitsu; Hanafusa, Toshiaki; Matsuzawa, Yuji
CS (1) Second Dep Intern. Med., Osaka Univ. Med. Sch., 2-2 Yamada-oka, Suita, Osaka 565 Japan
SO Diabetes, (1997) Vol. 46, No. 8, pp. 1381-1390. ISSN: 0012-1797.
DT Article
LA English
AB To clarify the regeneration process of **pancreatic** beta-cells, we established a new mouse model of diabetes induced by selective perfusion of alloxan after clamping the superior mesenteric artery. In this model, diabetes could be induced by the destruction of beta-cells in alloxan-perfused segments, while beta-cells in nonperfused segments were spared. Intraperitoneal glucose tolerance tests showed glucose intolerance, which gradually ameliorated and was completely normalized in 1 year with a concomitant increase of insulin content in the **pancreas**. Histological examination showed neo-islet formation in the alloxan-perfused segment and the **proliferation** of spared beta-cells in the nonperfused segment. In the alloxan-perfused segment, despite a marked reduction of islets in size and number at an early stage, both the number of islets, including islet-like cell clusters (ICCs), and the relative islet area significantly increased at a later stage. Increased single beta-cells and ICCs were located in close contact with **duct** cell lining, suggesting that they differentiated from **duct** cells and that such extra-islet precursor cells may be important for beta-cell regeneration in beta-cell-depleted segment. In addition to beta-cells, some nonhormone cells in ICCs were positive for nuclear **insulin promoter factor 1**, which indicated that most, if not all, nonhormone cells positive for this factor were beta-cell precursors. In the nonperfused segment, the islet area increased significantly, and the highest 5-bromo-2-deoxyuridine-labeling index in beta-cells was observed at day 5, while the number of islets did not increase significantly. This indicated that the regeneration of islet endocrine cells occurs mostly through the

proliferation of preexisting intra-islet beta-cells in the nonperfused segment. In conclusion, the regeneration process of beta-cells varied by circumstance. Our mouse model is useful for studying the mechanism of regeneration, since differentiation and **proliferation** could be analyzed separately in one **pancreas**.

L18 ANSWER 20 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTPACTS INC.DUPLICATE 10
AN 1997:202299 BIOSIS
DN PREV199799501502
TI Alpha-Cell neogenesis in an animal model of IDDM.
AU O'Reilly, Lorraine A.; Gu, Danling; Sarvetnick, Nora; Edlund, Helena; Phillips, Jenny M.; Fulford, Tony; Cooke, Anne (1)
CS (1) Dep. Pathology, Immunology Div., Univ. Cambridge, Tennis Court Road, Cambridge CB2 1QP UK
SO Diabetes, (1997) Vol. 46, No. 4, pp. 599-606.
ISSN: 0012-1797.
DT Article
LA English
AB Currently there is debate regarding the capacity of **pancreatic** islets to regenerate in adult animals. Because **pancreatic** endocrine cells are thought to arise from **duct** cells, we examined the **pancreatic ductal** epithelium of the diabetic NOD mouse for evidence of islet neogenesis. We have evidence of **duct proliferation** as well as **ductal** cell differentiation, as suggested by bromodeoxyuridine-labeling and the presence of glucagon-containing cells within these **ducts**. In addition, the **ductal** epithelia in diabetic NOD mice expressed the neuroendocrine markers neuropeptide Y and tyrosine hydroxylase. These **ducts** also expressed the homeobox gene product, insulin promoter factor 1. **Ductal** cell **proliferation** and expression of these markers was not observed in transgenic NOD mice (NOD-E), which do not develop clinical or histopathological symptoms of IDDM. This suggests that the observed **ductal** cell **proliferation** and differentiation was a direct result of beta-cell destruction and insulin insufficiency in these adult diabetic mice, which further suggests that these events are recapitulating islet ontogeny observed during embryogenesis. It is possible that comparable processes occur in the human diabetic **pancreas**.

L18 ANSWER 21 OF 21 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 11
AN 1996:216872 BIOSIS
DN PREV199698773001
TI **PDX-1** is required for **pancreatic** outgrowth and differentiation of the rostral duodenum.
AU Offield, Martin F.; Jetton, Tom L.; Labosky, Patricia A.; Ray, Michael; Stein, Roland W.; Magnuson, Mark A.; Hogan, Brigid L.; Wright, Christopher V. E. (1)
CS (1) Dep. Cell Biol., Vanderbilt Univ. Sch. Med., 1161 21st Avenue South, Nashville, TN 37232-2175 USA
SO Development (Cambridge), (1996) Vol. 122, No. 3, pp. 983-995.
ISSN: 0950-1991.
DT Article
LA English
AB It has been proposed that the Xenopus homeobox gene, XlHbox8, is involved in endodermal differentiation during **pancreatic** and duodenal development (Wright, C. V. E., Schnegelsberg, P. and De Robertis, E. M. (1988). Development 105, 787-794). To test this hypothesis directly, gene targeting was used to make two different null mutations in the mouse XlHbox8 homolog,pdr-1. In the first, the second **pdx-1** exon, including the homeobox, was replaced by a neomycin resistance cassette. In the second, a lacZ reporter was fused in-frame with the N terminus of **PDX-1**, replacing most of the homeodomain.

Neonatal **pdx-1**-/mice are apancreatic, in confirmation of previous reports (Jonsson, J., Carlsson, L., Edlund, T. and Edlund, H. (1994). Nature 371, 606-609). However, the **pancreatic** buds do form in homozygous mutants, and the dorsal bud undergoes limited **proliferation** and outgrowth to form a small, irregularly branched, **ductular** tree. This outgrowth does not contain insulin or amylase-positive cells, but glucagon-expressing cells are found. The rostral duodenum shows a local absence of the normal columnar epithelial lining, villi, and Brunner's glands, which are replaced by a GLUT2-positive cuboidal epithelium resembling the bile **duct** lining. Just distal of the abnormal epithelium, the numbers of enteroendocrine cells in the villi are greatly reduced. The **PDX-1**/beta-galactosidase fusion allele is expressed in **pancreatic** and duodenal cells in the absence of functional **PDX-1**, with expression continuing into perinatal stages with similar boundaries and expression levels. These results offer additional insight into the role of **pdx-1** in the determination and differentiation of the posterior foregut, particularly regarding the **proliferation** and differentiation of the **pancreatic** progenitors.

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